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Results of a BFM-Based Protocol for the Treatment of Childhood B-Non-Hodgkin's Lymphoma and B-Acute Lymphoblastic Leukemia in Argentina

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Purpose. To report the feasibility and results of a study based on the BFM-ALL-NHL/86 protocol for B-non-Hodgin's Lymphoma (NHL) and B-Acute Lymphoblastic Leukemia (B-ALL) in Argentina. *Design.* Prospective, single arm, non-randomized trial. *Patients and Methods.* From August 1988 to December 1993, 87 consecutive patients with B-NHL/B-ALL were admitted and 82 were eligible. The therapy was stratified according to stage. All patients received a cytoreductive prephase with cyclophosphamide and prednisone. Those with stage I-II were treated with three 5-day blocks of combined intense chemotherapy including dexamethasone, cyclophosphamide, ifosfamide, cytarabine, teniposide, doxorubicin, and 500 mg/m^2 of methotrexate as a 24 hour continuous infusion. Stage III received 6 blocks and those with stage IV/B-ALL received 6 intensified blocks in which 2 g/m^2 of 24 hour continuous infusion methotrexate and vincristine were added. Triple intrathecal therapy was given for CNS prevention. After the first two blocks the response was assessed and those with a partial response were offered optionallya second look surgery or local radiotherapy. *Results.* With a median follow-up of 38 (range 16–71) months, the event-free survival (pEFS) for the whole group was 0.69 (Stage I-II n = 16 pEFS = 0.94, stage III n = 50 pEFS = 0.66, Stage IV n = 7 pEFS = 0.43, B-ALL n = 9 pEFS = 0.66). Patients with stage III abdominal tumors who achieved a partial response by imaging studies after induction had a significantly higher risk of relapse than those with a complete response (p = 0.02). Relapse was the most frequent event Toxicity was mainly hematological. *Conclusions.* The application of this protocol was feasible in our setting and its results comparable to the German study. Patients with stage I-II had an excellent outcome. Those with stage III and B-ALL achieved an encouraging event-free survival, however those with abdominal tumors and partial response to induction chemotherapy fared less favourably. This strategy was less effective for patients with initial CNS disease. Med. Pediatr. Oncol. 28:333–341, 1997.

Key words: B-non-Hodgkin's Lymphoma; BFM protocols; pediatrics; therapy

INTRODUCTION

The prognosis of children with B-non-Hodgkin's lymphoma (B-NHL) has improved dramatically over the past years after the introduction of intensive chemotherapy regimens. In the early eighties, it was recognized that patients with advanced stage B-NHL should be treated with a different drug combination from that used in patients with non-B-NHL in order to achieve better results [1]. In 1981, the Berlin Frankfurt Münster (BFM) group introduced a new drug combination consisting of two different 5-day blocks of chemotherapy based on fractionated cyclophosphamide and methotrexate for patients with B-NHL with promising results [2]. In the succeeding BFM trials for B-NHL, the treatment duration was shortened and the dose-intensity was increased for patients with advanced stage B-NHL [3]. The ''Hospital de Pediatría Prof JP Garrahan'' was opened in 1987. In 1988 our group started this prospective study based on the ALL-NHL/BFM 86 protocol to treat patients with B-NHL. The objectives of this protocol were to determine the feasibility of the application of a BFM-based strategy for the treatment of these patients, tailoring their therapy according to the disease extension. In addition, patients with B-acute lymphoblastic leukemia (B-ALL) were scheduled to receive a specific therapy based on

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B-NHL-like treatment. The results of the therapy of patients with B-NHL and B-ALL in a single institution are the subject of this report.

PATIENTS AND METHODS

Patients

The study was opened on August 1988 and closed on December 1993. A total of 109 consecutive patients with NHL were enrolled. Twenty two had non-B-NHL and will not be reported here. Of a total of 87 patients with B-NHL, 82 were eligible. Cause of ineligibility included: wrong diagnosis of B-NHL in two patients. Both were diagnosed as probable B-NHL on morphological grounds and treated accordingly, but after relapses, complete immunophenotypical characterization was consistent with T-NHL. Two patients died shortly after admission without receiving any treatment and diagnosis of B-NHL was made post-mortem. One patient had received chemotherapy elsewhere before the admission to our center.

There were two protocol violations. One patient received the first three blocks of chemotherapy and his parents refused to continue for nonmedical reasons. The remaining one was erroneously undertreated (stage III treated as stage II). Both were considered eligible and survive event-free. Written informed consent was obtained from parents or guardians. This study was approved by our institutional clinical trial review committee.

Diagnosis

Cases were classified according to the National Cancer Institute Working Formulation for Clinical Usage [4]. The corresponding term for large cell anaplastic lymphoma in the working formulation is diffuse large cell lymphoma of immunoblastic type, but in this report we use the term large cell anaplastic lymphoma to describe this entity since it is included in the updated Kiel classification [5] and REAL classification [6] as a distinct clinicopathological entity. Patients were treated as B-NHL if they had one of the following features: small-noncleaved cell lymphoma, large cell NHL with B phenotype, large cell anaplastic lymphoma regardless of the immunophenotype, unclassified tumors with B phenotype, and those with FAB L3 cells. Patients with lymphoblastic NHL and B-precursor markers were excluded.

Diagnosis was based on cytomorphology in 16 cases. In all these cases, FAB L3 cells were detected and the production of surface immunoglobulin (slg) was evidenced by monoclonal antibodies. In the remaining 66 cases, the diagnosis was based upon histopathological findings. In addition, in 38 of them, the immunophenotype was consistent with a B-cell origin. In 25 patients, no immunophenotyping studies could be done. One patient with large cell anaplastic lymphoma had T-cell markers, and the remaining two had histiocyte and null phenotype respectively.

TABLE I. Differences Between the BFM-ALL-NHL/86 Protocol and the Present Study

Issue	BFM ALL-NHL/86 protocol	Present study
Treatment of stage II (not completely resected)	6 Blocks A,B,A,B,A and B	3 Blocks A,B and A
Treatment of patients with residual mass after induction	Second-look surgery and local radiotherapy if viable cells are detected	Second-look surgery or local radiotherapy both optionally
Methotrexate dosage in blocks AA and BB	5 g/m^2	2 g/m^2

All the histological preparations were analyzed and reviewed by the same pathologist (GG). The lymphoid origin of the tissue was confirmed by anti CD45 and the B phenotype was confirmed with pan-B monoclonal antibodies on paraffin sections, or on fresh tissue using a panel of commercially available reagents. CD30 was detected using Ber-H2 antibody on paraffin embedded tissue.

Staging

Murphy's staging system was used for clinical staging [7]. On admission, all patients underwent a lumbar puncture with microscopical examination of the cytocentrifugate, a bone marrow aspiration, a complete blood cell count, and imaging studies of the involved areas.

Serum LDH determination was not mandatory. Initial CNS disease was diagnosed if cerebral infiltrates were detected on a CT scan and/or any number of FAB L3 cells were found on the cytospin examination of the CSF. B-ALL was diagnosed when $\geq$25% of FAB L3 blasts were detected in the bone marrow.

Therapy

The treatment protocol was based on the ALL-NHL BFM 86 protocol for B-NHL with minor modifications [3] (Table I).

The therapy was stratified according to stage into three subgroups. Patients received ''state-of-the-art'' supportive care including hyper hydration, urine alkalinization, and allopurinol. Since 1992, the use of G-CSF or GM-CSF was allowed, however, it was not an essential component of the protocol. The decision on the use of G-CSF or GM-CSF in a given patient was based on the treating physician opinion and the drug availability. G-CSF or GM-CSF was started 24 to 48 hours after the end of chemotherapy and kept until absolute neutrophil count reached 1×10^9/L for 2 consecutive days after the ex-

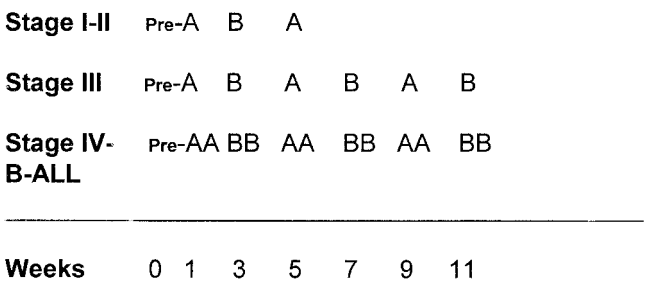

Fig. 1. Treatment schema (Pre = prephase, B-ALL = B-Acute Lymphoblastic Leukemia).

pected nadir. Dosage ranged from 5 to 10 μg/Kg/day and the drug was given subcutaneously.

All patients received a 5-day cytoreductive prephase consisting of prednisone and cyclophosphamide. Patients with stage I and II were treated with three blocks of combined intensive chemotherapy designated A,B, and A. Those with stage III received six courses A,B,A,B,A, and B. Patients with stage IV and B-ALL received an intensified therapy consisting of six blocks AA,BB,AA, BB,AA, and BB. The dosage and schedule of these blocks are depicted in Figure 1 and Table II. A minimum interval of two weeks was required to begin with the following cycle. After the hematological recovery of the second induction course, all patients underwent an imaging evaluation of all initially involved areas. Bone marrow aspiration and lumbar puncture were repeated at this point if they were positive at diagnosis. In case of partial response (PR), a second-look surgery was optional. Local radiotherapy (30 Gy) was optional for patients with partial response. No intensification of chemotherapy was scheduled for these patients.

Definitions

Complete remission (CR) was defined as the complete disappearance of all tumor masses as well as lymphoblasts in the bone marrow and/or CSF if present at diagnosis. Partial response was defined as a reduction greater than 25% of the tumor mass by imaging studies without disappearing completely. Initial tumor failure was defined as the persistence of lymphoblasts in the BM or the CSF and/or the progression of the local tumor whether or not it had decreased in size after the initiation of chemotherapy.

Relapse was defined as the recurrence of lymphoma with the same histological and/or immunophenotypical features as the initial one at any site after CR was achieved. Local relapse was diagnosed when the relapse involved a previously involved site (except bone marrow and CSF). Death on induction was defined as death of any cause after diagnosis and before the remission status could be evaluated.

Death from any cause after diagnosis, initial tumor failure, relapse, and second malignancies were defined as events.

Statistical Analysis

Event-free survival (EFS) and relapse probability were calculated according to Kaplan-Meier [8]. Differences were compared with the log-rank test [9]. Standard error and 95% confidence interval were calculated as reported by Peto and Greenwood respectively [10,11]. EFS time was calculated from the first day of chemotherapy to the day when an event occurred. Patients in whom no event occurred were censored at the day of the last contact. EFS of patients with initial tumor failure was calculated from the first day of chemotherapy to the day when progressive disease was diagnosed.

The cut-off date for survival analysis was September 1995.

Yates corrected Chi square analysis was used to calculate differences in proportions and Mann Whitney U-test was used to compare the absolute neutrophil count, days between each cycle, total duration of therapy, bacteremic, and febrile episodes per patient according to G-CSF administration.

RESULTS

Patients' Characteristics

Median age was 7 4/12 (range 1 to 19) years. The male to female ratio was 3.3/1. Three patients had stage I disease, 13 had stage II, and 50 had stage III disease. All stage IV (n = 7) had initial CNS invasion at diagnosis and two had additionally BM disease. Nine patients had B-ALL (one patient had concomitant CNS disease). The distribution of the primary site according to the stage is shown in Table III. Histological subgroups included: 44 cases of small non-cleaved cell lymphoma (32 Burkitt and 12 non-Burkitt type), 20 cases of large cell NHL (3 of them with large cell anaplastic lymphoma). Two cases were B-cell, unclassified.

Two patients with congenital HIV infection were included. One of them had B-ALL with a large unresectable abdominal tumor and achieved a continuous event-free survival after 40 months from diagnosis. The remaining one had a stage III abdominal tumor and died after 20 months of being disease-free because of an opportunistic infection. An additional patient with congenital hypogammaglobulinemia and a stage III abdominal NHL is in continuous event-free survival after 34 months of diagnosis. All patients with an immunodeficient status received the protocol without any modification.

Response to Induction Chemotherapy

Stage I and II: Three patients had all lymphoma manifestations completely resected at diagnosis and are therefore not evaluable for response. The remaining 13

TABLE II. Description of the Drugs, and Dosage of the Protocol

Prephase
Cyclophosphamide 200 mg/m^2/day IV. Days 1 to 5
Prednisone 30 mg/m^2/day. Days 1 to 5
Triple intrathecal therapy. Day 1
Block A
Dexamethasone 10 mg/m^2/day IV. Days 1 to 5
Methotrexate 500 mg/m^2/day. IV Day 1. Ten percent of the dose was given as a 30 minute bolus and the remaining 90% over a 23.5 hour infusion.
Leucovorin: 15 mg/m^2/dose. IV. Hours 48,51 and 54. After the start of the Methotrexate infusion.
Ifosfamide: 400 mg/m^2/day. IV. Days 1 to 5. One hour infusion.
MESNA: 400 mg/m^2/day IV. Hours 0,4, and 8 from the start of Ifosfamide infusion. Days 1 to 5.
Cytarabine: 150 mg/m^2/dose. IV. Thirty minutes infusion. Repeated every twelve hours. Days 4 and 5.
Teniposide: 100 mg/m^2/day. IV. One hour infusion. Days 4 and 5.
Triple intrathecal therapy. Day 1.
Block B
Dexamethasone 10 mg/m^2/day IV. Days 1 to 5.
Methotrexate 500 mg/m^2/day. Day 1. Ten percent of the dose was given as a 30 minute bolus and the remaining 90% over 23.5 hour infusion.
Leucovorin: 15 mg/m^2/dose. IV. Hours 48,51 and 54 after the start of the Methotrexate infusion.
Cyclophosphamide: 200 mg/m^2/day. IV. One hour infusion. Days 1 to 5.
Doxorubicin 25 mg/m^2/day. IV. One hour infusion. Days 4 and 5.
Triple intrathecal therapy. Day 1.
Block AA
Dexamethasone, Ifosfamide, MESNA, Cytarabine and Teniposide were given in the same dosage and schedule as in Block A.
Vincristine 1.5 mg/m^2/day. IV. (Max. dose 2 mg) Day 1. Bolus injection.
Methotrexate: 2000 mg/m^2/day. Day 1. Ten percent of the dose was given as a 30 minute bolus and the remaining 90% over 23.5 hour infusion.
Leucovorin: 15 mg/m^2/dose. Hours 36,42,48 and 54 after the start of the Methotrexate infusion.
Triple intrathecal therapy. Day 1.
Block BB
Dexamethasone, Cyclophosphamide and Doxorubicin were given in the same dosage and schedule as in Block B.
Vincristine 1.5 mg/m^2/day. (Max. dose 2 mg) Day 1. Bolus injection.
Methotrexate: 2000 mg/m^2/day. Day 1. Ten percent of the dose was given as a 30 minute bolus and the remaining 90% over 23.5 hour infusion.
Leucovorin: 15 mg/m^2/dose. Hours 36,42,48 and 54 after the start of the methotrexate infusion.
Triple intrathecal therapy. Day 1.
Patients with initial CNS invasion received 6 consecutive weekly doses of triple intrathecal chemotherapy starting from week 0.

Triple intrathecal therapy

Age (years)	Methotrexate	Cytarabine (dose in mg)	Dexamethasone
<1	6	16	2
1–2	8	20	2
2–3	10	26	4
3–9	12	30	4
>9	15	40	4

TABLE III. Primary Site According to the Disease Stage

	Abdomen	Peripheral lymph nodes	Mediastinum	Extranodal	Bone marrow[a]
Stage I-II	6	5	—	5	—
Stage III	39	3	4	4	—
Stage IV[b]	4	1	—	1	1
B-ALL[c]	5	—	—	2	2

[a]Patients in whom no other organ involvement could be detected.
[b]All patients had also CNS invasion at diagnosis.
[c]One patient had CNS invasion at diagnosis.

achieved a CR after the two cycles of induction chemotherapy.

Stage III. Two patients were not evaluable for response because they died on induction. The evaluation of response was inconclusive in 4 patients. Three children had an initial tumor failure. Eleven patients had a partial response to induction chemotherapy. A second look surgery was undertaken in 4 of them and persistent viable cells were detected in one case who subsequently died of progressive disease. The remaining three are alive in CR. Local radiation therapy was given to 2 patients with PR in whom resection of the residual mass was considered impossible. Both had abdominal primaries and received 30 Gy to the para-aortic area and 20 Gy to a pre-hepatic mass causing cholestasis respectively. The former died with progressive disease and the latter is alive and disease-free for 38 months. Thirty patients achieved a CR after induction chemotherapy.

Stage IV/B-ALL: One patient with stage IV was not evaluable for response he died on induction. All 6 patients evaluable for response of stage IV achieved a CR after induction chemotherapy. Two patients with B-ALL were not evaluable for response (one died on induction and one had an inconclusive evaluation). Two of 7 patients with B-ALL had persistent disease outside the bone marrow, however, no second look was done and both survive event-free. Five achieved a CR after induction chemotherapy.

Evaluation of Remission Status and Timing of Complete Remission

Remission status was evaluated by physical examination in 4 patients, by CT scan in 39 cases and by ultrasound in 21. Three patients achieved CR on diagnosis after the excision of the tumor mass. The information about the imaging procedure used to assess the tumor mass was not available in 5 cases.

Of 13 patients with partial response to induction chemotherapy, 4 achieved a complete remission after the third chemotherapy block, 1 after the fourth block, 4 after the fifth block, and 4 after the completion of therapy. In two of them a surgical excision of a residual mass showed no evidence of viable cells.

Event-free Survival

Median follow-up was 38 (range 16–71) months. Two patients were lost to follow-up after a minimum follow-up time of 16 months. The pEFS for the whole population was 0.69 (SE = 0.05, 95% confidence interval (CI) 0.60–0.76). The pEFS for patients with stage I and II disease was 0.94 (SE 0.06 95% CI 0.83–1), for stage III 0.66 (SE 0.06 95% CI 0.55–0.77), for stage IV 0.43 (SE 0.18 95% CI 0.28–0.58), and for B-ALL 0.66 (SE 0.15, 95% CI 0.47–0.75) (Figure 3). The probability of relapse for patients who achieved a complete response after induction chemotherapy was less than that for those patients who had a partial response {Relapse probability of patients who achieved a CR after two courses (n = 54), 0.21 (SE 0.05 95% CI 0.13 to 31); relapse probability of patients with PR after induction of chemotherapy (n = 15), 0.33 SE 0.05, (95% CI 0.24 to 0.42)}, but this difference did not reach statistical significance. When only patients with stage III abdominal tumors are analyzed, this difference becomes significant {relapse probability for patients who achieved a CR after induction chemotherapy = 0.17 (SE 0.07, 95% CI 0.04–0.30) and 0.5 (SE 0.17, 95% CI 0.34–0.66) for those with PR, $p = 0.02$}.

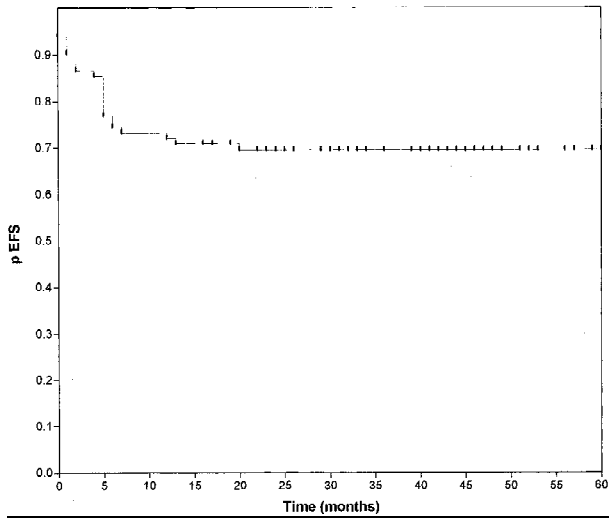

Fig. 2. Probability of event-free survival (pEFS) for the 82 patients with B-non-Hodgkin's lymphoma included in the study. Tick marks represent censored data.

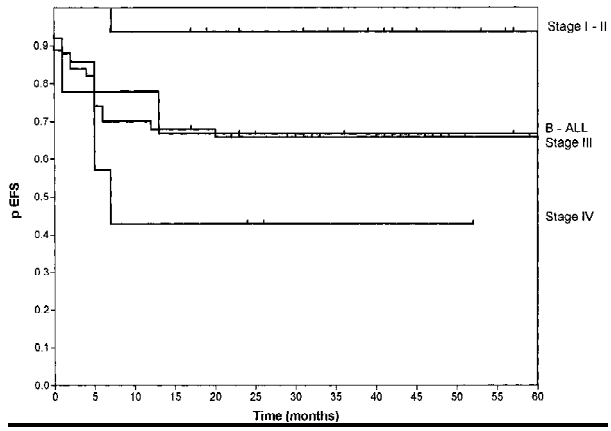

Fig. 3. Probability of event-free survival (pEFS) according to disease stage. Stage I and II disease = 0.94 (Standard error (SE) 0.06 95% confidence interval (CI) 0.83–1), stage III 0.66 (SE 0.06 95% CI 0.55–0.77), stage IV 0.43 (SE 0.18 95% CI 0.28–0.58), and B-ALL 0.66 (SE 0.15, 95% CI 0.47–0.75). Tick marks represent censored data.

Events

Adverse events according to stage are listed in Table IV. A total of 25 events occurred. Relapse was the most

TABLE IV. Description of Events According to Stage

	Stage I/II	Stage III	Stage IV	B-ALL
Patients	16	50	7	9
Events	1	17	4	3
Death on induction	—	2	1	1
Tumor failure	—	3	—	—
Relapse	1	10	3	2
Death in CR	—	2	—	—
Lost to follow-up	—	2	—	—
Alive and disease-free up to Sept '95	15	33	3	6

frequent event (16 patients). Relapse involved the primary site in 10 instances, either alone (n = 5) or combined with relapse at other sites (n = 5). These other sites included: bone marrow in 3, lymph nodes in 1, and pleural in 1.

The remaining relapses included: Isolated CNS relapse in a single patient without CNS invasion at diagnosis and in 3 patients with initial CNS invasion. In one additional stage IV patient with BM and CNS invasion at diagnosis, a combined BM and CNS relapse occurred. One patient with a liver primary had an isolated testicular relapse after 12 months from diagnosis which was retrieved by local radiotherapy and more intensive chemotherapy and is surviving in second CR after 39 months from relapse. All other patients who relapsed eventually died of progressive disease. Median interval from diagnosis to relapse was 5.3 months (range 2–12 months). Four patients died on induction. Two of them because of acute renal failure after tumor lysis and the remaining two died in aplasia of overwhelming sepsis. Three patients in stage III had initial tumor failure and eventually died of progressive disease. Two patients died in CR, one of them because of a septic episode during neutropenia and the remaining one died as a consequence of an opportunistic infection associated to congenital HIV infection 20 months after the diagnosis of NHL.

Results According to Histologic Subtypes

There were no significant differences in pEFS between the two major subgroups (pEFS for patients with small-non-cleaved cell NHL 0.70 (SE 0.1, 95% CI 0.51–0.80) and pEFS 0.71 SE 0.06 95% CI 0.6–0.82 for patients with large cell B-NHL). Three patients had a mediastinal large cell NHL with sclerosis [6]. Two of them achieved a long-term event-free survival and the remaining one had progressive disease after a partial response to induction chemotherapy and died of a cardiac tamponade. None achieved a complete remission by imaging studies after induction chemotherapy. In one case, the mass persisted up to the end of therapy. A second-look surgery was then done, but no viable cells were found and the patient is disease-free 21 months from diagnosis. Three patients had large cell anaplastic lymphoma. One of them had an initial tumor failure and died with progressive disease and the remaining two are in continuous event-free survival.

Extranodal

Eleven patients had their primary tumors in uncommon extranodal areas. Four of them were located in the Waldeyer ring, three had bone primaries and three had skin and subcutaneous tissue (two of them in the face); all survive event-free. The remaining patient had a liver primary and was described above.

Toxicity

World Health Organization (WHO) grade III/IV hematological toxicity occurred after most cycles in all patients, however only forty-three percent of them were followed by fever and neutropenia.

A comparative analysis of infectious complications and hematological toxicity in patients according to G-CSF administraton is shown in Table V. When patients receiving A-B blocks with G-CSF were compared to patients receiving A-B blocks without G-CSF, no statistically significant differences in ANC nadir, days between cycles, total duration of therapy, number of bacterial, or febrile episodes were seen. However, for the group of patients receiving AA-BB blocks, those who received CSF had higher ANC nadirs ($p = 0.02$), shorter days between cycles ($p = 0.07$) and shorter duration of therapy ($p = 0.05$) than those not receiving G-CSF. Twelve percent of them had a documented bacterial or fungal pathogen. One patient had grade IV CNS toxicity consisting of generalized seizures and reversible comma after the first administration of intrathecal chemotherapy which resolved with supportive care. The nutritional impact of the induction therapy for patients with stages III, IV and B-ALL was substantial. Moderate to severe malnutrition occurred in 34 cases. Sixteen patients received total parenteral nutrition and 31 were treated with enteral feeding through a nasogastric tube. Nevertheless patients with stage I and II tolerated the regimen relatively well and none received nutritional support. No cases of grade IV hepatic or renal toxicity were recorded. However, four patients with high tumor burden required hemodyalisis after the institution of chemotherapy because of tumor lysis. All had spontaneous tumor lysis which worsened after the initiation of therapy. One of them had kidney involvement at diagnosis. Three patients with large unresectable stage III abdominal tumors had a small bowel perforation during induction chemotherapy and were treated surgically. The median hospital stay for the whole patient population was 64 days (range 20 to 163).

DISCUSSION

Although earlier experience in treatment of NHL in our country has been published [12,13], this was the first

TABLE V. Comparative Analysis of the Hematological Toxicity and Infectious Complications According to Chemotherapy and Use of G-CSF

Chemotherapy blocks	A-B (without G-CSF)	A-B (with G-CSF)	*p*	AA-BB (without G-CSF)	AA-BB (with G-CSF)	*p*
Blocks number/patients number	185/44	48/7		32/7	39/7	
ANC Nadir ($X10^9$/L) median-(range)	0.55 (0–3.6)	0.8 (0–3.5)	.31	0.28 (0–2.8)	1.27 (0–3)	.02
Days between each cycle median (range)	20 (15–29)	20 (18–22)	.34	22.8 (20–25)	20.8 (18–21)	.07
Total duration of therapy (days) Median (range)[a]	109 (86–218)	110 (98–132)	.29	136 (109–156)	113 (98–126)	.05
Bacteremic episodes per patient[b] Mean (range)	0.4 (0–2)	0.14 (0–2)	.51	0.57 (0–2)	0.42 (0–1)	.82
Infectious deaths	2	0	.67	1	0	.97
Febrile episodes per patient. Median (range)	1.7 (0–6)	2.1 (0–3)	.31	3.1 (1–6)	2.4 (0–5)	.65

ANC = Absolute neutrophil count.

[a]Only patients with Stage III are included in the blocks A-B group.

[b]Total of episodes of fever with positive blood cultures in the total patient population for each group.

time that BFM protocols were given for these patients in our setting. This study shows that the application of the ALL-NHL BFM 86 protocol to treat patients with B-NHL is feasible in our setting and the results obtained were comparable to the German study in most instances, albeit in a smaller patient group [3]. The prognosis of patients with ALL improved substantially after the introduction of BFM protocols in our country [14]. These protocols proved to be effective, reproducible, and applicable in patients with ALL in our setting [14].

The clinical and molecular features of B-NHL in latin american children seem to be different from that of patients in Europe or the United States [15]. It has been reported that the response to moderately intense chemotherapy and overall survival are better in tropical Latin American countries [16,17]. Moreover, children with small non-cleaved cell lymphoma from tropical areas in Latin America also show different molecular features from children from temperate areas [15]. The median age for presentation of B-NHL is around 4 years in these countries [16,17]. In most studies from developed countries, the median age of these patients is 8 to 10 years [3,18,19]. In addition, it was suggested that children with B-NHL from Latin American countries present more frequently with an abdominal primary tumor [16]. Our patient population mostly lived in temperate areas, and seem to resemble more closely to that reported from developed countries, since both age and primary tumor distribution are comparable to most reports from these countries [3,18,19]. All these issues led us to believe that children from our area need to be treated with aggressive chemotherapy to improve their chance of survival.

The 5% induction death rate achieved in this study compares favorably to other contemporary studies [18,19]. However, in the German study, this figure is even lower [3]. This finding suggests that the use of a cytoreductive prephase with fractionated cyclophosphamide and prednisone is a safe initial treatment for these high-risk patients. Most induction deaths in our study occurred during the first year of the application of the protocol, therefore, it is likely that as supportive care improved in recent years in our setting, this complication might be now less frequent.

The outcome of patients with stage I/II B-NHL was excellent, since only one patient had a relapse. Earlier studies showed that this subgroup of patients achieve similar results after treatment with both B and non-B strategies [1]. Like the German report, these results were obtained after only 7 weeks of moderately intensive chemotherapy. Interestingly in our study, unlike the German study [3], we treated all patients with stage II disease with this regimen regardless of the resectability of their primary tumor with excellent results.

The results in children with stage III B-NHL were encouraging since over two thirds of them survived. The response rate to induction chemotherapy is comparable to the BFM report. In our study, patients who achieved a partial response after the first two induction studies had a significant higher risk of relapse. Unfortunately, since few patients underwent a second-look surgery, it was not possible to determine the prognostic importance of persistent viable cells in residual masses. The value of radiotherapy or surgical resection of a persistent mass is questionable and very few patients in our study were treated with these modalities to make any conclusion. A recent report from the BFM group suggested that the intensification of chemotherapy in patients with incomplete response to induction therapy may improve the results [20]. Our own results in patients with B-ALL show that the outcome of patients with a high tumor burden can be improved with intensified chemotherapy. Moreover, patients with B-ALL fared as good as those with stage III in our study, and this phenomenon can be explained by the drug intensification given to this subgroup of patients. In our study the dose of Methotrexate was 2 g/m^2 in patients who received the intensified arm. This dose is

lower than that used in the original BFM report (5 g/m^2) and was apparently not associated to a substantial increased risk of systemic or CNS relapse. Furthermore, our overall low CNS relapse rate in patients without initial CNS involvement confirm previous reports which suggested that preventive cranial irradiation is not necessary in these patients [3,21].

On the other hand, patients with overt CNS disease at diagnosis fared less favourably in our study and the results achieved were comparable to the German report [3]. This seems to confirm the unfavourable prognosis of patients with initial CNS disease [22,23]. A study from the SFOP (French Pediatric Oncology Society), showed that even though the outcome of patients with advanced B-NHL could be improved with intensive chemotherapy, only 4 of 21 patients with initial CNS invasion survived [22]. Likewise, a study from the Pediatric Oncology Group found similar results with 10 of 21 patients alive [23]. However, a recent preliminary report from the BFM group obtained a 68% event-free survival of patients with initial CNS disease with an intensification of chemotherapy together with the use of higher doses of methotrexate or cytarabine, and intraventricular chemotherapy [24]. In a more recent study from the SFOP, encouraging results were obtained using an intense regimen without intraventricular chemotherapy but using cranial radiotherapy [25].

This strategy was equally effective for all histopathological subtypes analyzed. Patients with large cell B-NHL fared like those with small non-cleaved cell NHL. Even though most large cell anaplastic lymphoma show T phenotype, this protocol proved to be effective for the treatment of this condition [26] and for mediastinal large cell lymphoma with sclerosis [3], so we followed this rationale. Four of six patients with this condition achieved a continuous event-free survival in our study. However, this number of patients is too small to draw any conclusion. In addition many patients with less common extranodal localizations were included in our study. Accordingly, the event-free survival rate was 100% for patients with Waldeyer ring, bone, and subcutaneous B-NHL. However the number of patients in each category is small.

Our data support previous observations that suggested that this strategy is effective for patients with extracerebral B-NHL occurring in children with HIV infection [27], since both our two cases achieved a long-lasting CR, even though they had advanced disease at diagnosis. Unfortunately one of them died disease-free because of an opportunistic infection predisposed by the immune deficiency of HIV infection.

The toxicity and cost of this protocol was high, more specially so for a developing country with limited resources. Most patients with advanced disease had severe nutritional and infectious complications. The prophylactic use of G-CSF was reported effective in reducing the interval between chemotherapy cycles, in decreasing the number of episodes of fever, neutropenia, and culture confirmed infections in patients with high-risk ALL treated with the ALL-BFM 90 protocol [28]. The present study was not designed to assess these issues in a prospective randomized fashion. Nevertheless, we found that patients who received prophylactic G-CSF in the intensified arm were less likely to have bacteremic episodes and febrile neutropenia, however this difference was not statistically significant. It is noteworthy that no patient receiving G-CSF died of infection, however other factors such as improvement of supportive care may have played a role. The delays in the beginning of each cycle was a common feature in our study, mainly because hematopoietic toxicity, infections, and mucositis. In the subset of patients receiving the intensified arm, the use of G-CSF allowed an earlier administration of the chemotherapy protocol and therefore promoted a tighter adherence to the treatment schedule increasing the dose-intensity of the regimen. The relative value of the use of this drug in this setting must be validated in prospective randomized studies.

It is therefore imperative to find new, effective, and less expensive therapeutic interventions to reduce the overall cost of treatment of children with B-NHL in this setting. The early identification of patients with a low risk of relapse who may be cured with less aggressive therapy and of those with high-risk disease who may benefit from an intensified therapy would certainly help to achieve this goal.

We conclude that the application of a modified version of the ALL/NHL BFM 86 protocol is feasible in our setting with comparable results, however, patients with stage III, especially those with abdominal tumors and residual mass after induction chemotherapy may benefit from a more intense regimen. Those with CNS disease fared less favourably with this protocol and new therapeutic interventions should be explored.

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